REMARKS

Applicant acknowledges the Examiner's modification of the previous restriction requirement to be a restriction and election of species requirement. Applicant hereby elects Group I and the species PP1 and PP2 for examination on the merits.

Attached hereto is a document captioned "Version With Markings To Show Changes Made" which is a marked-up version of the amendments made to the claims.

Also submitted herewith is a Petition Under 37 CFR §1.136(a) and §1.17(a) requesting a one-month extension of time for reply and a check for $110.00 to cover the required fee.

Claims 1-4 and 16-20 are currently pending in the application.

Claims 3-4 and 19-20 were objected to for using abbreviations PP1 and PP2 without reciting the full terminology for which they are used. Claims 3-4 and 19-20 have been amended to eliminate these informalities, as suggested by the Examiner.

Claims 1-4 and 16-20 have been rejected under 35 U.S.C. §103(a) as being obvious over the combination of a number of references. In order to establish a *prima facie* case for obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974). Furthermore, there must be a teaching in the references themselves that would have motivated one of skill in the art to combine the references, with a reasonable expectation of success, at the time the invention was made. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed, Cir. 1991). Neither prong of this analysis has been satisfied in this instance.

Claims 3-4 and 19-20 have been rejected under 35 U.S.C. §103(a) as being obvious over any one of van Bruggen *et al.*, Aiello *et al.* (US 6,284,751), or Jirousek *et al.* (US 6,093,740) in view of Munshi *et al.*

Van Bruggen *et al.* describe methods of treating edema formation in a mouse brain by administering a truncated Flt-1 receptor fused to a Fc-IgG, which reportedly inhibits VEGF signaling. The reference does not teach or suggest treatment of vascular edema with a Src family tyrosine kinase inhibitor as presently claimed.

Aiello *et al.* teach methods of inhibiting VEGF stimulated capillary permeability, such as associated with pulmonary edema, using a β-isozyme selective protein kinase C (PKC) inhibitor (see Abstract). The reference teaches that the "expression of VEGF is controlled by multiple mechanisms" (col. 8, lines 40-41). Aiello *et al.* do not teach or

suggest methods or articles of manufacture for ameliorating tissue damage related to vascular leakage or edema by contacting the tissue with an effective amount of a Src family tyrosine kinase inhibitor as required by claims 1-4 and 16-20 of the present invention.

Jirousek *et al.* teach methods of reducing or inhibiting VEGF stimulated vascular permeability using a β-isozyme selective inhibitor (see Abstract). Jirousek *et al.* do not teach or suggest methods or articles of manufacture for ameliorating tissue damage related to vascular leakage or edema by contacting the tissue with an effective amount of a Src family tyrosine kinase inhibitor.

While Munshi *et al.* disclose a relationship between Src family protein tyrosine kinases and VEGF signaling with relation to proliferation of Kaposi Sarcoma cells, the reference does not provide any insight into vascular edema. In fact, Munshi *et al.* , like Aiello *et al.*, teach that the VEGF signaling pathway is a complex system. For example, Munshi *et al.* report that inhibition of cSrc affected MAP kinase activity but not Flk-1/KDR, a primary VEGF receptor protein (see Munshi *et al.*, p. 1173, col. 1, last sentence).

A person of ordinary skill may have found it obvious to try the applied combination, but that is not the standard of 35 U.S.C. §103(a). There must be some teaching, suggestion, or incentive supporting the combination. *In re Geiger*, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); *In re Fine*, 5 USPQ2d at 1598. That is not the case here. Given the complexity of the VEGF signaling pathway, at best there is an invitation to experiment without any expectation of success.

Claims 3-4 and 19-20 have been rejected under 35 U.S.C. §103(a) as being obvious over any one of van Bruggen *et al.*, Aiello *et al.*, or Jirousek *et al.* in view of Hanke *et al.* and either of He *et al.* or Cooke *et al.*

Van Bruggen *et al.*, Aiello *et al.*, and Jirousek *et al.* were discussed above. None of theses references disclose the connection between Src family tyrosine kinase inhibitors and vascular edema.

Hanke *et al.* teach that pyrazolopyrimidines PP1 and PP2 are potent inhibitors of selected members of the Src family of tyrosine kinase inhibitors. In particular, Hanke *et al.* teach that PP1 and PP2 are selective inhibitors of Lck and FynT, and that these tyrosine kinases are involved in lymphocyte function (page 695, col 2, 2nd full paragraph). The "Results" section of the reference, beginning at col. 1 of page 697 and continuing through the first paragraph of col 1, page 698, discloses that, whereas PP1 and PP2 are potent inhibitors of

Lck and FynT (IC_{50} of 4-6 nM for both inhibitors against both enzymes), PP1 is significantly less effective against Src (IC_{50} 170 nM) and non-Src family tyrosine kinase EGF-R (IC_{50} 250 nM) and completely ineffective against non-Src family tyrosine kinase inhibitors ZAP-70 and JAK2 (IC_{50} > 100 μM and > 50 μM, respectively). Thus, Hanke *et al.* teach that inhibition of protein tyrosine kinases is an unpredictable art, and that the effectiveness of PP1 and PP2 against Src family tyrosine kinase inhibitors, in particular, is variable and not predictable. Hanke *et al.* do not teach or suggest that vascular permeability and edema can be ameliorated by administration of a Src family tyrosine kinase inhibitor, as claimed in the present invention.

He *et al.* teach that VEGF induces nitric oxide production, which can be blocked by inhibition of Src kinase. This study does not address vascular permeability. He *et al.* utilized a battery of drugs, such as PP2, to identify which ones block VEGF-induced nitric oxide production in cultured cells. There is no suggestion in the reference to utilize a Src kinase inhibitor to treat vascular permeability.

Similarly, Cooke *et al.* teach that PP2 inhibits VEGF stimulated VE-Cadherin tyrosine phosphorylation, but provide no insight into vascular permeability. There is no suggestion in the reference itself that VE-Cadherin bears any relationship to vascular permeability or edema.

None of the possible combinations of Aiello *et al.* with Hanke *et al.*, Jirousek *et al.* with Hanke *et al.*, nor van Bruggen *et al.* with Hanke *et al.* teaches or suggests that vascular permeability and edema can be ameliorated by administration of a Src family tyrosine kinase inhibitor, as claimed in the present invention. Neither He *et al.* nor Cooke *et al.* cures this deficiency. None of the references discloses the connection between inhibition of Src kinases and vascular permeability.

In order to render the claims of the present invention obvious, each and every limitation of the claims must be found in the cited references, along with a motivation for one of skill in the art to combine the references with a reasonable expectation of success. One of skill in the art would not have been motivated to combine these references to obtain the result achieved by the present invention, since there is no connection made in the references between Src inhibition and vascular permeability. As such, claims 1-4 and 16-20 are patentable over the cited prior art and the rejections should be withdrawn.

Claims 3-4 and 19-20 have been rejected under 35 U.S.C. §103(a) as being obvious over any one of van Bruggen *et al.*, Aiello *et al.*, or Jirousek *et al.* in view of Hanke *et al.* and Eliceiri *et al.* (1998).

The Examiner generally states, on page 9 of the Office Action, that Eliceiri *et al.* teach that Src kinase is required for VEGF signaling pathways. Applicant respectfully submits that this is an overly broad interpretation of the reference. In fact, Eliceiri *et al.* teach that there is a requirement for Src activity in a particular VEGF pathway, e.g., VEGF induced angiogenesis. This teaching of Eliceiri *et al.* is disclosed in the present application, and is the subject matter of the parent PCT and provisional applications of the present application. Eliceiri *et al.* do not teach or suggest that vascular permeability and edema can be ameliorated by administration of a Src family tyrosine kinase inhibitor, as required in the present claims

The present application is a continuation-in-part of PCT/US99/11780, which in turn, claims priority from U.S. Provisional Application for Patent Serial No. 60/087,220. The Examiner has stated, on pages 9-10 of Paper No. 10, that none of the claimed prior applications teach the use of small organic chemical inhibitors of Src family tyrosine kinases and in particular PP1 and PP2 for treatment of conditions related to vascular leakage or edema as is currently claimed and that the present claims have not been given the benefit of the earlier filing date. Applicant submits, however, that the present application is entitled to such a priority date of 29 May 1998 for subject matter included in the application that was also disclosed in the provisional application. The priority provisional application discloses the entire subject matter of Eliceiri *et al.*, and has a filing date 5 months prior to the November 1998 publication date of Eliceiri *et al.* Therefore, Eliceiri *et al.* is not citable as a reference against the present application. The exclusion of Eliceiri *et al.* as a reference renders the present rejection moot, and the rejection should be withdrawn.

Conclusion

None of the references cited against the present application, either alone, or in combination teaches or suggests methods or articles of manufacture for ameliorating tissue damage related to vascular leakage or edema by contacting the tissue with an effective amount of a Src family tyrosine kinase inhibitor as required by claims 1-4 and 16-20 of the present invention.

Reconsideration and allowance of claims 1-4 and 16-20 is solicited.

Respectfully submitted,

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Amendments to the Claims:

Claim 3 has been amended to read:

3.(amended) The method of claim 2 wherein said chemical inhibitor is selected from the group consisting of pyrazolopyrimidine PP1, pyrazolopyrimidine PP2, PD173955, AGL1872, PD162531, Radicol R2146 and Geldanamycin.

Claim 4 has been amended to read:

4.(amended) The method of claim 3 wherein said inhibitor is pyrazolopyrimidine PP1.

Claim 19 has been amended to read:

19.(amended) An article of manufacture of claim 18 wherein said Src family tyrosine kinase inhibitor is selected from the group consisting of pyrazolopyrimidine PP1, pyrazolopyrimidine PP2, PD173955, AGL1872, PD162531, Radicol R2146 and Geldanamycin.

Claim 20 has been amended to read:

20.(amended) An article of manufacture of claim 18 wherein said Src family tyrosine kinase inhibitor is pyrazolopyrimidine PP1.